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Technology
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BORDEN'S REVIEW of NUTRITION RESEARCH

Summaries and reviews of research information concerning the nutritive values of milk and milk products. Published by The Borden Company, 350 Madison Avenue, New York, N. Y.

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THE NEWER KNOWLEDGE OF MILK IN THE MANAGEMENT OF PEPTIC ULCER

Modern civilization exacts a toll in the form of numerous human ills stemming largely from the hectic turbulence and nervous strain of everyday living. Peptic ulcer has long been prominent in the list of these ills, statistics indicating this disease occurs at some time in at least 12 per cent of all adults. Recent reports indicate that strife, violence, fear and anxiety accompanying present war-time conditions, are causing a striking all-time high in the incidence of peptic ulcer. Such reports from England and continental Europe reveal an alarming increase of ulcer in the armed forces and also in the civilian population, while medical authorities in the United States are preparing to meet a similar situation.

The treatment of peptic ulcer has usually involved correction of the associated conditions of hyperacidity and nervous strain. Recently, attempts have been made to correlate the incidence of ulcer, in some measure at least with dietary deficiencies. Results of animal experiments along these lines have been highly favorable. Investigators have actually been able to produce gastric ulcers in laboratory animals, in some cases, by means of a diet lacking the milk proteins casein and lactalbumin. In addition, they were able to prevent ulcers by the inclusion of these proteins in the diet of other animals. The possibility is not at all remote that milk proteins or other proteins will assume vital importance in peptic ulcer prevention and therapy in human beings.

In the light of these discoveries relating the use of casein and lactalbumin to the prevention of experimental peptic ulcer, new significance is attached to the classical dietary treatment of ulcer with milk (fresh, powdered or evaporated) and cream; and also to the use of other bland dairy products, rich in milk protein, such as cream cheese, cottage cheese, and ice cream in those diets.

What Is Known About Peptic Ulcer?

The term peptic ulcer is given to certain characteristic lesions of the mucous membrane of the stomach and duodenum. Although many years of in-

vestigation have been devoted to the study of the disease, its ultimate causes still remain obscure. A number of aggravating factors immediately involved in the disturbance, however, have been recognized and it is toward their alleviation that present methods of treatment have been directed. Those factors most frequently associated with peptic ulcer are erosive action of the gastric juice and emotional or nervous strain.

Effect of Gastric Fluids: Food material which has been partially broken down by mastication and admixed with salivary secretions enters the stomach where it is further acted upon by the gastric juice. The digestive properties of the gastric juice are due chiefly to the enzyme pepsin which functions only in the presence of sufficient hydrochloric acid.

Under the influence of certain abnormal stimuli, the flow of gastric juice may be either inhibited or excessively stimulated. In either case, the results are detrimental to proper digestion. In the present instance, we are concerned with what happens when too much gastric juice is secreted, or more specifically, when the concentrations of hydrochloric acid and pepsin in the gastric juice are abnormally increased. Often, nothing more severe than temporary distress considered as some form of "indigestion" or "heart burn" occurs. Under some conditions, however, the gastric juice may actually attack tissues of the stomach wall itself as well as the food. This may be due in part at least, to excess acid in the gastric juice, to an increase in the activity of the pepsin, or to a failure of the mucous lining to adequately protect the stomach walls. (Normally, the stomach walls are protected from such digestive attack by a layer of mucous [mucin]). The problem that has puzzled investigators in this field for many years is concerned with the explanation of why the gastric juice causes ulcers in certain cases and not in others. The two-fold aspect in this problem of the interactions between gastric juice and stomach wall has been termed by Rivers (1) "aggression and defense," and poses the following questions:

1. What is responsible for the heightened eroding powers of the gastric juice in certain instances?

and

2. What is responsible for the lowered resistance of the stomach tissues to the attack of acid or pepsin in the gastric juice in certain instances?

These questions still remain unanswered. It may be that future research on the interplay of these two factors will disclose the ultimate causes of peptic ulcer.

Effect of Emotional and Nervous Strain: The importance of the psychic factor in disease generally and in the incidence of peptic ulcer specifically, is being recognized and stressed more than ever by medical authorities. Cannon (2) in discussing the role of emotion in disease some six years ago, stated that a highly significant change has occurred in the relative incidence of disease; serious infectious

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diseases which formerly had been wide-spread and frequently disastrous have decreased or almost disappeared while diseases and disabilities predicated upon excessive strain of the nervous system have increased. More recently, in 1941, in an editorial commenting upon the effect of war on the incidence and recurrence of peptic ulcer, Crohn (3) states:

> "The concept of peptic ulcer as a psychosomatic disease is rapidly gaining ground and apparently with good reason. Whether psychic influences, raising gastric acidity, actually cause ulcer is somewhat problematical, but no experienced clinician and no student of psychology could today deny the influence of psychic imbalance and emotional upset upon the course and recurrence of ulcer."

The psychic stimuli created by the war are undoubtedly largely responsible for the very significant recent increase in peptic ulcer. Early in 1939 came the first reports of an increase in ulcer in Finland, both behind the lines and in the civilian population. Crohn goes on to state that letters and news items from England indicate a vast increase in the ulcer problem there; that a 35% increase has been reported in continental Europe; and, according to medical authorities, that peptic ulcer has taken the lead as the chief cause of medical disability among British and Canadian soldiers. Crohn concludes:

> "If the emotional balance and psychic equipoise of the civilian population *of our own country* are not on a much higher plane than that in wartime Europe, we may expect a large increase in the incidence of ulcer. . . ."

Dramatic confirmation of the long-suspected influence of emotional states on the development of ulcer was announced only a few weeks ago in October, by Wolf and Wolff (4). Such confirmation was made possible through actual observations of the interior of a man's stomach during various emotional states. The subject, an otherwise normal person, customarily fed himself through an artificial opening into the stomach made necessary by a childhood accident permanently sealing the esophagus. This opening permitted observation of the behavior of the stomach wall. Various measurements were made of the activity of the stomach and these were correlated with the carefully noted mental states and emotional reactions of the subject. The result, a fascinating picture of the effect of emotion on the activity of the stomach, revealed that mental distress involving anxiety, hostility, or resentment was immediately reflected in a flushing of stomach tissues with blood and a marked increase in acid content of the gastric juice. These symptoms disappeared promptly upon relief from the disturbed mental states. Sustained emotional upset over a period of days or weeks was accompanied by gastric disturbances resulting in the development of numerous bleeding points and erosions upon the slightest irritations. Such areas, upon prolonged contact with the acid gastric juice, soon developed into actual ulcers. Wolf and Wolff summarized their observations as follows:

> "Emotional conflict involving anxiety, hostility, and resentment was accompanied by accelerated acid secretion, hypermotility, and engorgement of the gastric mucosa.

"Intense sustained anxiety, hostility and resentment were accompanied by severe and prolonged engorgement, hypermotility and hypersecretion in the stomach. In this state mucosal erosions and hemorrhages were readily induced by even the most trifling traumas, and frequently bleeding points appeared spontaneously as a result of vigorous contractions of the stomach wall.

"Contact of acid gastric juice with such a small eroded surface in the mucous membrane resulted in accelerated secretion of acid and further engorgement of the whole mucosa. Prolonged exposure of such a lesion to acid gastric juice resulted in the formation of a chronic ulcer."

These studies clearly establish the importance of the psychic factor in the genesis of peptic ulcer. The development of ulcer in the absence of emotional symptoms, however, indicates that still other factors are involved.

Other Contributing Factors: In the interplay of "aggression and defense" reactions in the development of peptic ulcer, consideration must be given to other possible predisposing factors. These may include local irritation (trauma) resulting from inadequate mastication of food, vigorous muscular contractions, or ingestion of irritating substances; impaired general health; overeating, irregular eating, poorly balanced diet; excessive drinking and smoking; constitutional or hereditary predisposition, etc.

Impairment of mucin formation, constituting a deficiency in the tissue defense mechanism, may be yet another cause in the chain of events leading to peptic ulcer. According to Manville (5) this may be brought about by deficiencies of proteins or of glucuronic acid, both of which are essential for the synthesis of protective mucin. In cases of active infection, when toxins may be accumulating in the body, there is likely to be a shortage of glucuronic acid because this substance is essential for the detoxication of such poisons. In the detoxication process the available supply of glucuronic acid is used up and as a consequence the formation of mucin is hindered. Unless sufficient glucuronic acid is supplied in food (apple pectin and hemicelluloses) or unless more protein food is supplied as a source of amino acids for the synthesis of glucuronic acid, mucin formation will suffer and the inadequately protected stomach walls will be exposed to the erosive action of gastric juices.

Treatment: Treatment of peptic ulcer centers mainly around the alleviation of the most obvious aggravating conditions — the abnormally erosive gastric juice and disturbing psychic influences. An effort is made to remove or reduce causes of mental uneasiness. If these persist, treatment of the physiological causes will constantly be counteracted and to some extent, nullified. Alkalis or other acid-binding agents are administered to neutralize the excessive acidity (the bicarbonate addict is well-known) . Various chemical or physiological means are employed to inactivate the pepsin. Smooth, bland foods are given to prevent irritation. Demulcent coating agents are administered in an effort to protect the ulcerated surfaces from the acid-pepsin-containing gastric juice. Prominent among such demulcents are mucin, derived from secretions of healthy mucous

lining of animal stomachs, (6, 7, 8) and colloidal aluminum hydroxide, a compound which is effective also in neutralizing excess acid and is thought to inactivate pepsin by precipitating it from the gastric juice (8). Recent isolation of an acid-inhibiting hormone, entero-gastrone, from the human stomach may afford additional control of the acid factor in ulcer (9). None of these methods of treatment, however, deals with the fundamental causes of ulcer; they are primarily means of affording relief — frequently only temporary.

Relation of Diet to Peptic Ulcer

The fact that ulcerative lesions might be related in some way to a deficiency in diet was demonstrated in 1923 by Pappenheimer and Larimore (10). They observed that rats maintained on an experimental diet designed to produce rickets and composed largely of white flour, frequently developed stomach ulcers. The presence in the stomach of such irritants as swallowed hairs increased the incidence of ulcers in these animals. The experimental diet was deficient in the quality of its protein, in vitamins A and D, and in the bone-building minerals calcium and phosphorus. Irradiation of the animals in amounts sufficient to prevent or cure the rickets had no marked effect in relieving the ulcerative condition. Likewise, the addition of cod liver oil, of mineral salt mixtures, or of yeast extract had little curative effect when administered separately (11). However, when all of the essential nutrients were provided at the same time in a complete and well-balanced diet, the ulcers did not develop. Pappenheimer and Larimore concluded that stomach ulcers, under their experimental conditions, could be entirely prevented when the diet was adequate in all nutritional essentials.

Investigations by others led to the observation (1931) that casein, the principal protein of milk, prevented ulcers consistently developed by animals on a low protein diet (12). Irritants such as steel filings induced ulcers only when the diet was inadequate, particularly in the quantity and quality of protein (13). As a result of these observations, Hoelzel and da Costa (12) concluded that either a deficiency of protein or the lack of sufficient acid-binding protein in the diet might be a factor in the development of some cases of gastric or duodenal ulcer in man. The interrelationship of protein intake, its biological quality and the incidence of peptic ulcer was borne out by the work of a number of other experimenters during the next few years (14, 15). In the meantime many theories were advanced purporting to correlate the incidence of peptic ulcer with deficiencies in vitamins. The experimental evidence, however, was inconclusive and inadequate in support of the theories advanced.

The Sippy Diet: The effects of dietary factors on the incidence of peptic ulcer are closely related to the methods empirically devised for the treatment of the disease. Long before any studies were made on the possible relation of specific factors to the incidence and cure of peptic ulcer, Sippy introduced his now widely-used diet for the treatment of ulcer. This procedure, offered in 1915, after

Sippy had tested it clinically for more than twelve years (16) with excellent results, was based on his belief that the failure of an ulcer to heal was due to the corrosive action of the gastric juice, which could be prevented by neutralization of the hydrochloric acid. The chief features of the treatment were rest, washing out of the stomach, large amounts of milk and cream, and the administration of alkalizing medicinals. The Sippy milk and cream diet, with the administration of alkaline powders between feedings has formed the basis of many treatments devised since that time and in use at present.

Newer Knowledge of the Role of Protein In the Treatment of Peptic Ulcer

As a result of experimental findings over many years interrelating diet with the incidence of ulcer, and with the realization that the basic component of the widely successful Sippy treatment is milk, the significance of milk and its inherent proteins became increasingly apparent. Studies by Matzner, Windwer and Sobel (17) led to the conclusion that proteins exert a far greater protective power against the development of gastric lesions in animals than either carbohydrates or fats; their results, condensed and expressed statistically, show that under the test conditions, the following rates of ulcer incidence occurred with diets high in protein, carbohydrate and fat, respectively:

	Incidence of Gastric Lesions
high protein diet	10%
high carbohydrate diet	70%
high fat diet	73%

They considered the exhaustion of pepsin by protein the most probable explanation of the favorable effects with high protein diets (18). Whether the pepsin or the free hydrochloric acid content of the gastric juice plays the dominant role in ulcer formation is still a debatable question (18, 19, 20). Abnormally high amounts of both are found in the gastric juice of ulcer patients and without doubt each is a complementary and aggravating factor.

The theories advanced by Matzner and co-workers in explanation of their favorable results obtained with proteins, and the investigations of Hoelzel and da Costa (12, 13), Weech and Paige (15), and others are based on well-established physical and chemical properties of proteins. These investigators postulated that proteins protected the mucosa against destructive action of the gastric juice by neutralizing excess acid and inactivating excess pepsin:

1. Neutralization of Excess Hydrochloric Acid

Proteins, because of their acid-binding properties act as alkalis in an acid medium and are thus capable of combining with and neutralizing the hydrochloric acid in the gastric juice. Thus the concentration of free hydrochloric acid is reduced and its erosive action on stomach tissues diminished.

Inactivation of Pepsin

Pepsin is a proteolytic, or protein-digesting, enzyme. By introducing large amounts of protein material, the excess pepsin is provided with material to digest and is thus used up before it can exert its effect on the stomach walls.

Pepsin, like all other enzymes, is inactivated even when all other conditions are favorable, by the accumulation of the end products of digestion. Thus proteins may prevent further activity of pepsin as they are digested, by giving rise to enzyme-retarding digestion products.

Pepsin may be inactivated by an unfavorable change in the acidity of the gastric juice. The presence of hydrochloric acid is necessary for optimum peptic activity; if the acid is removed or reduced by combining with protein, sub-optimal conditions for the digestive action of pepsin result.

Because of their pronounced antacid and pepsin-retarding properties, proteins exert a beneficial influence in controlling the acid-pepsin factor, thus preventing ulcer formation or retarding destructive digestion of an already ulcerated area.

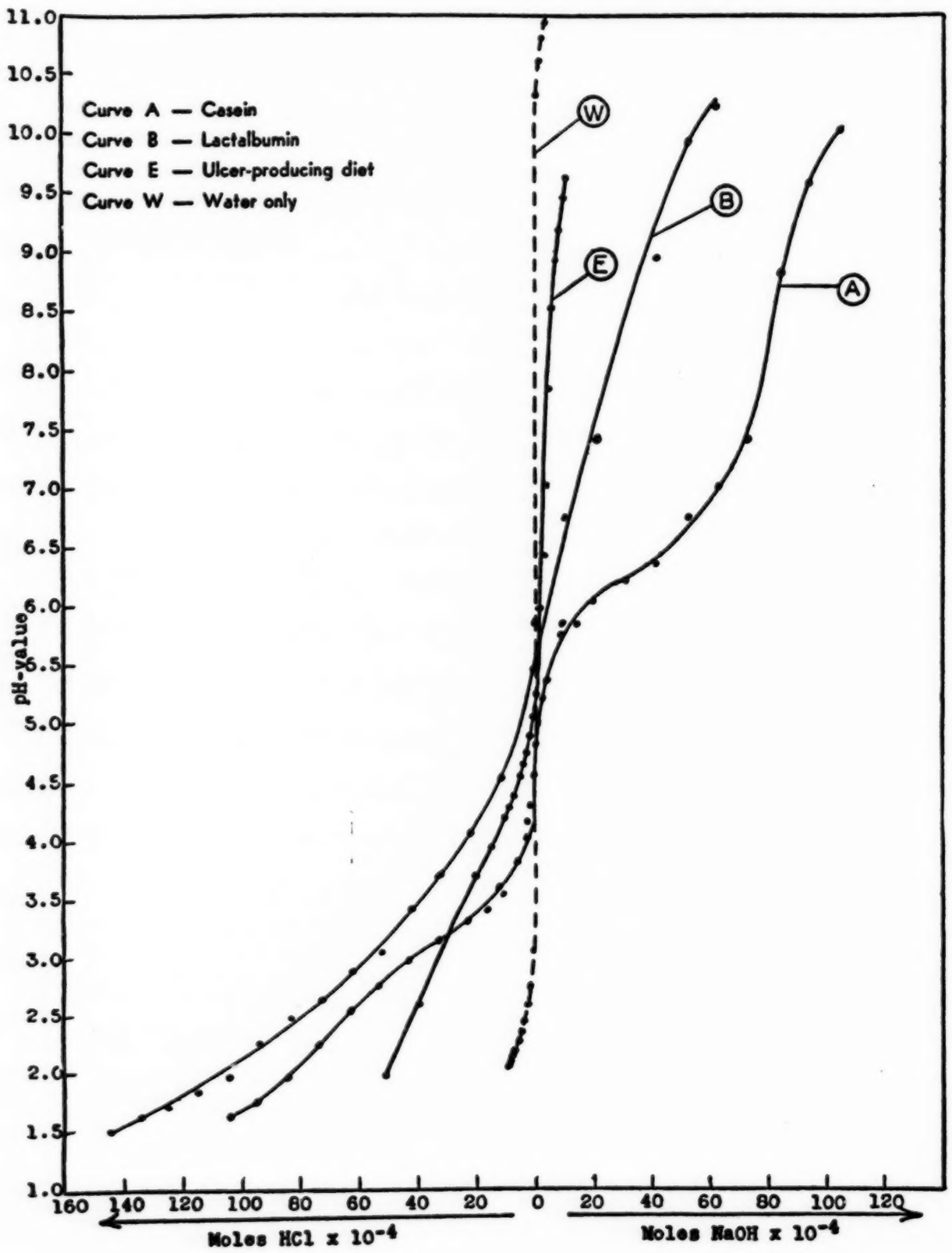
Effect of Milk Proteins (Casein and Lactalbumin): Carrying the research on proteins still further, and bearing in mind the basic importance of milk in ulcer therapy, Supplee and co-workers at the Borden Biological and Chemical Laboratories in Bainbridge, New York reported during the early part of this year highly favorable results on the prevention of peptic ulcer in experimental animals, with casein and lactalbumin, the proteins specific to milk (21). These investigations, as yet unpublished, took into account the nature of biologic faults resulting from a deficiency of vitamin A, the vitamin B complex and more particularly the specific character and quantity of the protein. A deficient diet, based on the ulcer-producing rations prepared by Sharpless (22), was employed and appropriately supplemented with each of the vitamin and protein variables involved in the studies.

Results of these interesting experiments indicated that, of all the factors tested, only casein and lactalbumin were effective in preventing experimentally induced ulcer. While the addition of various vitamin supplements to diets containing either casein or lactalbumin enhanced the growth effects obtained, the vitamins (with the exception of vitamin A) apparently exerted little if any influence upon the incidence of the ulcerative lesions. The proteins from rice polishings, unlike the proteins of milk, exerted no measurable specificity in preventing the ulcer pathology.

An interesting feature of these investigations involved the direct correlation of the acid-binding properties of casein and lactalbumin as determined *in vitro* with the degree of gastric acidity in the stomachs of the experimental animals following administration of the test diets. Animals fed the ulcer-producing diet containing little or no protein, and which showed slight or no acid-binding properties, exhibited a uniformly higher degree of gastric acidity than animals whose diets had been supplemented either with casein or lactalbumin. (These

proteins exhibit relatively high acid-binding properties from *in vitro* measurements) . The experiments revealed that the relative incidence of stomach lesions under the test conditions, can be closely correlated with the acid-binding properties of the diet as measured *in vitro* and the actual degree of acidity present in the stomachs of experimental animals. The greater the acid-binding properties of the milk protein or protein-carrying dietary, the lower the gastric acidity during digestion, and the lower the incidence of ulcer lesions. Experimental evidence indicated that the acid neutralizing properties of the milk proteins are as effective in reducing the gastric acidity of animals with active lesions as for those in which peptic ulcer had been prevented by the prophylactic action of protein.

Amount of Free Hydrochloric Acid Bound by Experimental Ulcer-Producing Diet and by Casein and Lactalbumin*



Following closely upon this experimental animal work come recent reports by other scientists of similar investigations with human subjects. These inves-

*Unpublished data—Borden Biological and Chemical Laboratories.

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tigators report successful control of stomach acidity and inhibition of peptic activity in a large group of human subjects through the feeding of a mixture of amino acids derived from the hydrolysis of the milk protein casein (23). On the basis of the favorable results obtained, further work is now in progress on the clinical treatment of peptic ulcer with a casein hydrolysate.

The Influence of Vitamin A in Conjunction with Milk Proteins: The investigations carried out at the Borden Laboratories are of further significance in indicating the relation of dietary factors to the incidence of experimental peptic ulcer. The milk protein, casein, while most effective in preventing ulcers when supplied in adequate amounts, was found to be further augmented in its prophylactic effect when supplemented with liberal amounts of vitamin A. A lower percentage of casein in the diet supplemented with additional vitamin A was as effective in wholly preventing ulcers as higher amounts of this protein with a lesser amount of vitamin A. It is well known that lack of sufficient vitamin A will cause pronounced changes in the protective epithelium of many parts of the body tending to weaken such tissues and thus subject underlying tissues to infection. In view of this fact, it is quite possible that insufficient vitamin A may be a primary factor in the lowered resistance of gastric epithelium to the attack of pepsin and hydrochloric acid with subsequent formation of ulcerative lesions.

Conclusion:

In the dietary treatment of peptic ulcer, milk and cream have long been recognized as the most important of all foods. According to McLester (24):

> "Milk always comes first. It should be the sole food in the beginning, the mainstay of the diet as treatment proceeds and an important adjunct to the menu for many years after a 'cure' has been obtained."

As supplementary foods are added to the basic milk and cream diet, it is significant that soft cheeses such as cottage cheese, the solids of which are practically all milk protein, cream cheese, ice cream, powdered milk and other protein dairy products constitute major ingredients in the dietary.

Findings of recent investigations stress the prophylactic and therapeutic properties of milk proteins in the efficient prevention and treatment of peptic ulcer. Thus science has explained the basis for the classic milk dietary in peptic ulcer developed by medical experience through years of clinical practice.

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NEWS DIGEST

BUTTER is superior to vegetable fats in its growth-promoting properties. This fact was revealed by recent research on milk substitutes such as "filled" milk often used in infant feeding. Such milk substitutes are made by the addition of some fat other than butter fat to skimmed milk. Laboratory tests were conducted on skimmed milk in which corn, coconut, cottonseed or soybean oil had been homogenized and to which vitamin A sufficient to equal that supplied by butter fat had been added. Comparison of the "filled" milks containing vegetable fats with milk containing butterfat showed an increased rate of growth for animals receiving the butterfat.

—1001

CANNED HAM AND EGGS is among the newer products developed for use by United States armed forces. The product which has recently been perfected after months of experimentation is chopped to a delicate consistency, prepared in commercial kitchens and canned. It is served after heating the can and is reported to be equally as palatable as its well-known home-prepared counterpart. The new product is designed to provide a canned food high in protein.

—1002

VITAMIN E, long regarded as the "anti-sterility" vitamin, may have only a secondary connection with the reproductive function. Recent investigations indicate the primary function of vitamin E is its influence on muscle metabolism. Derangement of normal muscle metabolism due to insufficient vitamin E may result in muscle dystrophy.

—1003

SWEETENERS are being developed from a number of new sources. The most recent of these is the apple. It has long been known that apple syrup is sweet, but its use has been limited because of its marked flavor. Food scientists have now been able to remove the flavor, color and stickiness from apples to produce a very sweet, bland syrup which can be used for sweetening ice cream, candies, and which may eventually even be used for icing cakes. Inasmuch as the syrup can be prepared from otherwise unmarketable apples, the supply of fresh apples is not affected.

—1004

SYNTHETIC RIBOFLAVIN, produced cheaply from paper mill waste is a new achievement. D-ribose, a comparatively rare sugar which is necessary for the synthesis of riboflavin and which formerly cost about $18,000 a pound, can be isolated from ordinary baker's yeast. This yeast in turn can be grown economically on sulfite liquor, a paper and pulp mill waste which is now being dumped into rivers. Two plants in Canada are already producing such low-cost yeast needed for the ribose-from-yeast process, and the erection of similar plants in the United States after the war is contemplated.

—1005

SKIM MILK, CHEESE, and DRIED WHEY should be used in increasing quantities for cheaper and improved human nutrition, urge nutrition authorities. Skim milk, either in liquid or powdered form, contains all the nutritive elements of whole milk, with the exception of those of the butterfat. Yet, despite its high food value and fairly low cost, only 12% of skim milk production has been used for human consumption. Cheese, too, is very rich in important vitamins, minerals, protein, and fat. The high consumption of cheese and other dairy products by the pastoral people of Asia and the Balkans is believed to be a major factor in the characteristic vigor and longevity of these peoples. Whey, a by-product of dairy manufacture, is an extremely potent source of vitamins and minerals, but until now has been diverted chiefly to animal feeding. One suggestion as to its use for human consumption is the enrichment of beverages such as popular soft drinks.

—1006

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MOLYBDENUM, a well-known industrial mineral, has now been isolated in traces from milk. Whether or not molybdenum is significant in animal or human nutrition is still being investigated—its essentiality for certain plants, notably tomatoes, has already been established. Analyses reveal that cows' milk contains approximately 46 to 50 micrograms per quart of this substance which may conceivably soon be allied with other trace minerals such as copper, cobalt, manganese, etc. whose essential role in nutrition has only recently been recognized.

—1007

MILK CASEIN derivatives have been used with remarkable results in the control of malignant high blood pressure, according to medical reports. The material is administered by injection and is said to effectively control this form of high blood pressure over a relatively long period.

—1008

MODIFIED PECTINS recently developed by industrial food chemists now make possible the production of low-sugar jellies which lend themselves to a wide variety of uses. These include the making of fruit salads and jellied consommes which remain firm at room temperature; wine jellies that are not too sweet; and ready to use aspics.

—1009

BIOTIN, one of the newly recognized components of the vitamin B complex, has emerged from the realm of the obscure with the very recent announcement of its chemical structure. Biotin is sometimes termed the "super-vitamin" because of its exceedingly high potency. It is important in poultry feeding and its significance in human nutrition is indicated. With the discovery of the chemical nature of this vitamin, of which only minute amounts have been isolated, it is expected that the way will be paved towards its synthesis by research chemists. The chemical name of biotin is 2'keto-3,4-imidazolido-2-tetrahydrothiophene-*n*-valeric acid.

—1010

VITAMIN C has assumed new importance in the war effort. Its loss through perspiration renders troops in tropic war subject to heat prostration a condition which can be prevented, as shown by industrial use of ascorbic acid administered to workers laboring under very hot conditions. Supplementation with vitamin B_1 and salt, which are also lost in perspiration, has further aided in the prevention of heat prostration. Vitamin C has also been found advantageous in combating the effects of shock caused by injury, operations, blood transfusions, and allergy such as hay fever. The close association of vitamin C with the health of intercellular tissue renders this vitamin especially helpful in promoting rapid healing of wounds. Its ability to detoxify such poisons as benzene, toluene, T.N.T., lead and zinc indicates its use in industrial war plants may be of great value.

—1011

MILK SOLIDS added to white bread result in a bread of even higher nutritive value than bread to which synthetic riboflavin and calcium have been added, according to recent nutrition experiments. Bread fortified with 6% milk solids is found to equal whole wheat bread in nutritive value; and the addition of this amount of milk solids to whole wheat flour produces a bread definitely superior to whole wheat bread itself. It was found that animals fed bread made with milk solids stored more riboflavin and retained more nicotinic acid (added as synthetic ingredient) and more thiamin. The best bread, it has been found, is that enriched with synthetic thiamin, niacin, and iron, and containing, in addition, nutritive milk solids.

—1012

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